

REMARKS

The invention relates to the identification and characterization of two classes of bone marrow stem cells, small and rapidly self-renewing stem cells (RS cells), and large, more mature marrow stromal cells (mMSC cells). The invention also relates to methods of their use.

Claims 1 through 10 are pending in the present application. Claims 4-8 and 10 have been withdrawn from consideration as being drawn to a non-elected invention. Therefore, claims 1-3 and 9 are currently under examination.

Claims 1 and 9 have been amended herein to recite a homogenous population of small and rapidly self-renewing stem cells. Support for the amendments to claims 1 and 9 is found throughout the as-filed specification as fully set forth below. As such, no new matter has been added by way of the present Amendment.

Further, claim 9 has been amended merely to incorporate the subject matter of claims 7 and 8, and to be in independent form. As such no new matter has been added by way of this amendment.

Rejection of Claims 1-3 and 9 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 1-3 and 9 under 35 U.S.C. § 102(b) as being anticipated by Bruder et al. (1997, J. of Cell. Biochem. 64:278-294; Bruder). Specifically, the Examiner is of the opinion that Bruder teaches a population of human mesenchymal stem cells (hMSC) and that the population of mesenchymal stem cells would thereby include the cells of the present invention. Therefore, the Examiner contends that claims relating to the expression of FLK-1, TRK, transferrin receptor, and annexin II would be considered an inherent property of the population of cells disclosed in Bruder. Applicants respectfully submit that Bruder does not anticipate the present invention for the following reasons.

It is hornbook law that “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). “The identical invention must be shown in as complete detail as is contained in the . . . claim.” *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added)). Therefore, Bruder must describe each and every element of claims 1-3 and 9, in order to anticipate these claims under 35 U.S.C. §102(b), and this

reference does not.

Applicants respectfully point out that Bruder describes a population of human mesenchymal stem cells (hMSC) isolated from bone marrow obtained from a donor, and that the hMSC-enriched low density fraction was initially plated at 10^7 nucleated cells per 60 cm^2 . Bruder estimates that the initial density of adherent hMSCs is approximately 1 in 10^5 of the total cell population, which therefore would correspond to 100 adherent hMSC in a 60 cm^2 dish. Thus, from the methods described in Bruder, it is clear that the cells of Bruder are a mixed population of adherent and non-adherent cells. Furthermore, Bruder also teaches a method of enriching a population of the adherent hMSCs by cultivating the cells for serial passage. As a result of the multiple serial passages, Bruder is able to obtain a population of adherent hMSCs. However, nowhere does Bruder teach that the adherent hMSCs can further be separated into at least two more population of cells: 1) small and rapidly self-replicating cells (RS cells) and 2) larger, mature marrow stromal cells as claimed in the present application.

Applicants respectfully submit that the mixed population of cells disclosed in Bruder is not a homogenous population of cells, as recited in claim 1 and dependent claims therefrom and in claim 9 following entry of the present Amendment. That is, claims 1 and 9 have been amended herein to recite a homogenous population of RS cells. Support for a homogenous population of RS cells is found throughout the specification. For example, beginning on line 24 of page 1, the specification discloses that the present invention encompasses a large number of homogenous cells useful in gene therapy applications. Further, beginning on line 14 of page 6, the specification teaches a method of preparing a purified fraction of RS cells from a mixture of cells containing larger, mature marrow stromal cells. Therefore, Applicants contend that the amendments to claims 1 and 9 relating to a homogenous population of RS are fully supported by the as-filed specification and overcomes the Examiner's rejection of the claims under 35 U.S.C. § 102(b).

Applicants further point out that the present invention relates to the novel discovery that the cells of the present invention express unique polypeptides and methods of isolating these cells using the unique polypeptides. That is, following entry of the present Amendment, the claims relate to a homogenous population of small and rapidly self-renewing stem cells based on their unique expression of selected polypeptides. Support for the amendments to the claims relating to a homogenous population of cells is found beginning on

line 18 of page 7, wherein the specification teaches that the RS cells of the present invention contain four epitopes not found on larger, mature marrow stromal cells, for example VEGF receptor-2(FLK-1), TRK (an NFG receptor), transferrin receptor, and annexin II (lipocortin 2). Further, the specification beginning on line 3 of page 4 teaches a series of polypeptides which can be used to isolate and distinguish the cells of the present invention. Applicants contend that nowhere does Bruder teach these unique polypeptides as features that characterize the cell disclosed therein. Therefore, in view of the present amendments to the claims, Bruder cannot anticipate the present invention because Bruder does not disclose each and every element of the claimed invention. Reconsideration and withdrawal of the Examiner's rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §102(b) is respectfully requested at this time.

Rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 1-3 and 9 under 35 U.S.C. § 102(b) as being anticipated by DiGirolamo et al. (1999, Brit. J. of Haematology 107:275-281; DiGirolamo). The Examiner opines that DiGirolamo teaches a population of human marrow stromal cells with high colony-forming efficiency and replicative potential and would therefore include the cells of the present invention.

Applicants respectfully contend that DiGirolamo does not teach the claimed invention as recited in the claims following entry of the present Amendment for the same reasons discussed above to overcome the rejection of the claims over Bruder and although they are not repeated here, they are equally applicable to the present rejection. Specifically, DiGirolamo does not teach each and every element of a homogenous population of small and rapidly self-renewing bone marrow stem cells. Further, DiGirolamo does not teach the unique polypeptides expressed by the small and rapidly self-renewing bone marrow stem cells. Therefore, Applicants hereby respectfully request that the rejection of claims 1-3 and 9 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection of claims 1-3 and 9 pursuant to 35 U.S.C. §102(a)

The Examiner has rejected claims 1-3 and 9 pursuant to 35 U.S.C. §102(a) as being anticipated by Colter et al. (2000, PNAS 97:3213-3218; Colter). Specifically, the Examiner contends that Colter discloses a cell type referred to as recycling stem cells or RS-2

cell, wherein the RS-2 cells are present in a population of isolated human marrow stromal cells. Thus, the Examiner reasons that the expression of the particular polypeptides recited in the as-filed claims are considered an inherent property of the cells.

Preliminarily, Applicants point out to the Examiner that as indicated on the first page of Colter et al., this reference was published online before the print date of March 28, 2000. That is, Colter et al. was available online on March 21, 2000. Therefore, any arguments presented herein in response to the Examiner's rejection of claims 1-3 and 9 under 35 U.S.C. §102(a) as being anticipated by Colter et al. is in view of the online publication date of March 21, 2000. Colter is therefore a 102(b) reference with respect to the present invention.

Applicants respectfully contend that Colter does not anticipate the claimed invention following entry of the present Amendment for the same reasons given to overcome the rejection of the claims over Bruder and DiGirolamo, although they are not repeated here, they are equally applicable to the present rejection. That is, claim 1 and dependent claims therefrom and claim 9 have been amended herein to recite a homogenous population of small and rapidly self-renewing stem cells (RS), wherein the cells express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2). Applicants assert that Colter does not teach a homogenous population of cell expressing these novel polypeptides and therefore cannot anticipate the present invention because Colter does not teach each and every element of the claims. Specifically, Colter does not teach a homogenous population of small and rapidly self-renewing stem cells wherein the cells express the unique polypeptides disclosed in the as-filed specification. Rather, Colter teaches a heterogeneous population of cells. For example, Colter teaches beginning on page 3214 that the **two** population of cells were seen in stationary cultures...most of the cells were large...there was a minor population of small and agranular cells...staining with propidium iodide demonstrated that about 98% of the cells in **both** populations were viable. In view of the foregoing arguments, Applicants hereby respectfully contend that Colter does not teach a homogenous population of cells and therefore request that the rejection under 35 U.S.C. § 102(a) be reconsidered and withdrawn.

Summary

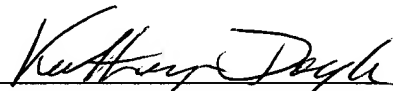
Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-3 and 9 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

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Enclosure: Petition for Extension of Time and fee therefor